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Food and Drug Administration
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Silver Spring, MD 20993-0002

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Attention: Beverly Friedman

This is in regard to the application for patent term extension for U.S. Patent No. 5,362,718 (the '718 patent) filed by Wyeth LLC under 35 U.S.C. § 156 on July 24, 2007, and forwarded to the Food and Drug Administration (FDA) on January 7, 2008. The request for patent term extension of the '718 patent is based on the regulatory review of the human drug product TORISEL® (temsirolimus). In the United States Patent and Trademark Office's (USPTO) letter of July 24, 2007, the USPTO identified that temsirolimus was an ester of sirolimus. Sirolimus is a human drug product known as RAPAMUNE®, which was approved by FDA in 1999. The USPTO's letter indicated that because TORISEL® was an ester of a previously approved base, the '718 patent would not be eligible for patent tern extension, because the approval of TORISEL® did not comply with 35 U.S.C. § 156(a)(5)(A).

In May of 2010, the Federal Circuit decided that an ester of a previously approved human drug product could support term extension even in light of a previous approval of a product containing the same "active moiety." In other words, the requirement in section 156(a)(5)(A) that the permission for the commercial marketing or use of the product claimed in the patent must be the first permitted commercial marketing or use was met where a drug substance, formulated as an ester (Metvixia), is approved after an approval of the same drug substance formulated as a salt (Levulan). See *Photocure v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010). In *Photocure v. Kappos*, 603 F.3d 1372 (Fed. Cir. 2010), the court relied on its previous decision in *Glaxo v. Quigg,* 894 F.2d 392 (Fed. Cir. 1990) (*Glaxo II*) for its determination of eligibility of Photocure's Metvixia product. Specifically, the Federal Circuit in *Photocure* stated that "[i]n *Glaxo* this court held that 'product' in §156(a) means the product that is present in the drug for which federal approval was obtained," *Id.* at 1376. (citing to *Glaxo II* at 894 F.2d at 393–95). Thus, *Glaxo II* is highly instructive in determining when an active ingredient, which may contain the same active moiety as a previously approved active ingredient, is eligible for extension.

In *Glaxo II*, the Federal Circuit affirmed the district court's determination that a patent which claimed an ester of cefuroxime was eligible for extension regardless of previous approvals of two salts of cefuroxime. *Glaxo II* at 393. Although the *Glaxo II* court did not explicitly set forth its rationale for determining that the patent was eligible for extension under section 156, in affirming the district court, the Federal Circuit implicitly adopted the district court's rationale. There, the district court in *Glaxo v. Quigg*, 706 F. Supp 1224 (E.D. Va. 1989) (*Glaxo I*) framed the rationale for eligibility as:

> the question sharply presented is whether the "product" referred to in (a)(5)(A) is cefuroxime axetil, on the one hand, or cefuroxime, the

> parent acid on the other. The answer to this question turns on the statutory definition of "product." Subsection (f) of Section 156 defines "product" as "a drug product," which, in turn, is defined as follows:
>
> > (2) The term "drug product" means the active ingredient of a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act) including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.
>
> *35 U.S.C. §156(f)(2).*
>
> The central question then is whether the active ingredient of Ceftin Tablets is the ester cefuroxime axetil or the parent acid cefuroxime. If the former is true, plaintiff is entitled to an extension of its patent term. If the latter is true, then no extension would be warranted because the FDA has previously approved NDA's for Zinacef and Kefurox, two sodium salts of cefuroxime.

Glaxo I at 1227.

Additionally, the *Photocure* court pointed out that they held in *Hoechst-Roussel Pharms., Inc. v. Lehman*, 109 F.3d 756, 759 (Fed. Cir. 1997) that "[f]or purposes of patent term extension, this active ingredient must be present in the drug product when administered." *Photocure* at 1376. Thus, the active ingredient of Photocure's Metvixia product is methylaminolevulinate hydrochloride, because that is the substance physically present in the final dosage form.

Applying the *Hoeschet* and *Glaxo I* analyses here, as articulated by the *Photocure* court, the active ingredient of TORISEL® is temsirolimus because that is the substance physically present in the final dosage form. Neither it, nor any salt or ester of temsirolimus has been previously approved by FDA. Because no salt or ester of temsirolimus had been approved prior to the approval of TORISEL®, the grant of permission to commercially market or use TORISEL® is the first permitted commercial marketing or use of the product/active ingredient as required by section 156(a)(5)(A). Accordingly, the '718 patent is eligible for extension under the provisions of section 156.

In light of the above analysis, applying the *Photocure* holding here, please confirm that the approval of TORISEL® constitutes the first permitted commercial marketing or use of the product in compliance with 156(a)(5)(A) and determine the applicable regulatory review period in accordance with section 156(d)(2)(A).

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
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Office of the Associate Commissioner
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RE: TORISEL® (temsirolimus)
Docket No.: FDA-2008-E-0102